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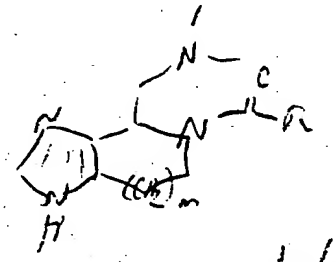
(54) Title: USE OF HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY PAIN

(57) Abstract

Azacyclic and heterocyclic derivatives having kappa agonist activity are useful in the treatment of inflammatory pain.



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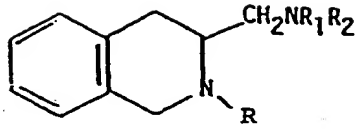
# USE OF HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY PAIN

The present invention relates to the use of certain compounds for the manufacture of medicaments for the treatment of inflammatory pain; to a method of treatment of inflammatory pain; and to pharmaceutical compositions for the treatment of such pain.

EP-A-228246, 232612, 232989, 260041, 261842, 275696, 330360, 333315, 333427, 361791, 370732, 409489, WO 91/08205, WO 91/08206, WO 91/17116 and WO 91/17981 (all Dr. Lo. Zambeletti S.p.a.) describe classes of heterocyclic derivatives which exhibit kappa receptor agonism and are of potential therapeutic utility as analgesics.

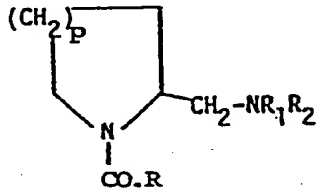
It has now been found that compounds of these classes activate peripheral kappa opioid receptors located on sensory nerve terminals. Activation of such receptors can lead to a reduction in the release of neurogenic inflammatory mediators released from the nerve terminals and to a reduction in transmission of nociceptive information to the CNS. Compounds of the present invention are, therefore, of potential use as peripheral analgesics in the treatment of a range of inflammatory painful conditions - such as arthritis and low back pain - since they may reduce both the causes and consequences of local inflammation.

According to the present invention there is provided the use of a compound, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of inflammation pain, wherein the compound is selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV) or (XVI):



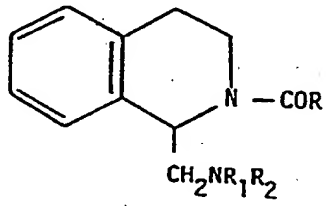
(I)

in which R is an acyl group containing a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring and $R_1$ and $R_2$ are independently $C_{1-6}$ alkyl groups or together form a $C_{3-6}$ polymethylene or alkenylene group;



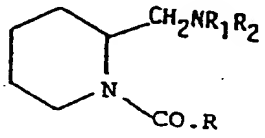
(II)

in which R, $R_1$ and $R_2$ are as defined for formula (I), and p is 1, 2, 3 or 4;



(III)

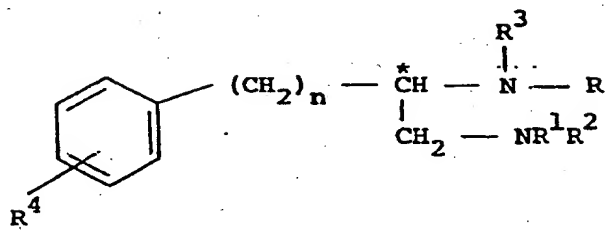
in which R, $R_1$ and $R_2$ and as defined for formula (I);



(IV)

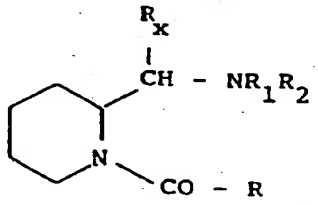
in which R is a group:

in which $R_3$ is Br, $NO_2$ or $CF_3$; and $R_1$ and $R_2$ are as defined in formula (I);



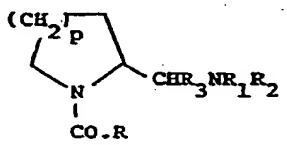
(V)

in which R is as defined in formula (I);
$R^1$ and $R^2$ each independently represents an alkyl, alkenyl or alkynyl group or $R^1$ together with $R^2$ represents a $C_{3-6}$ polymethylene or alkenylene group;
$R^3$ represents hydrogen or alkyl;
$R^4$ represents hydrogen, halogen, alkyl, hydroxy, alkoxy, nitrile, nitro, amino or mono or disubstituted amino; and
n represents 0 or 1;



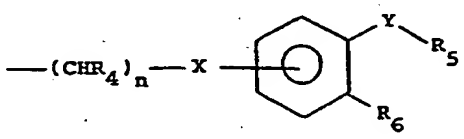
(VI)

in which R is as defined in formula (I);
$R_1$ and $R_2$ are independenlty hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{4-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl or together form a $C_{2-6}$ polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a hetero-atom, provided that $R_1$ and $R_2$ are not simultaneously hydrogen;
Rx is $C_{1-6}$ alkyl or phenyl, or Rx together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;



(VII)

in which $R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups, or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group optionally substituted with a hetero-atom, provided that $R_1$ and $R_2$ are not simultaneously hydrogen;
$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl, or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;
p is 1, 2, 3 or 4, and
R is a group of formula



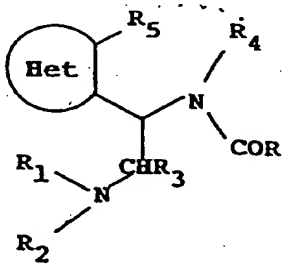
in which the group $-(CH_4)_n-X-$ is in the meta- or para-position with respect to $YR_5$ or $R_6$, $R_4$ is hydrogen or $C_{1-6}$ alkyl;

n is 0, 1 or 2;

X is a direct bond, or O, S or $NR_a$ in which $R_a$ is hydrogen or $C_{1-6}$ alkyl;

Y is >C=O, >CHOH.>S=O or $>SO_2$;
each of $R_5$ and $R_6$ is $C_{1-6}$ alkyl, or

$R_5$ and $R_6$ are linked together and $R_5$ represents $-(Z)_m-$ where m is 0 or 1 and Z is O, S or $NR_7$ where $R_7$ is hydrogen or $C_{1-6}$ alkyl;
and $R_6$ represents $-(CH_2)_q-$ where q is an integer of from 1 to 4, and in which one or more of the $-(CH_2)-$ groups is optionally substituted by a $C_{1-6}$ alkyl group;




(VIII)

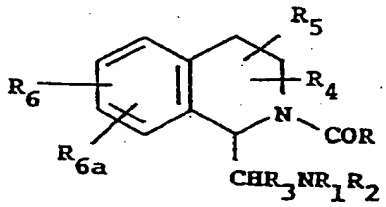
in which R is as defined in formula (I)
$R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a heteroatom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

$R_4$ is $C_{1-6}$ alkyl, or phenyl;

$R_5$ is hydrogen or together with $R_4$ forms a $-(CH_2)_n-$ group in which n = 1, 2 or 3; and

'Het' is an optionally substituted single or fused ring heterocyclic group, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;




(IX)

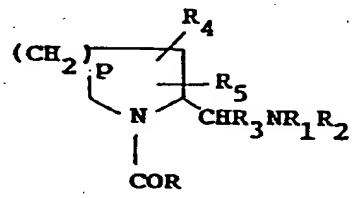
in which R is as defined in formula (I) and $R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group optionally substituted with a hetero-atom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl or $R_3$ together with $R_1$ forms a $-(CH_2)_3-$ or $-(CH_2)_4-$, group;

$R_4$ and $R_5$, which may be the same or different and may be attached to the same or different carbon atoms of the isoquinoline nucleus, are each hydrogen, halogen, hydroxy, $C_{1-6}$ alkyl, aryl, or $R_4$ together with $R_5$ form a $-(CH_2)_p$ group, where p is an integer of from 1 to 5 and one or more of the $-(CH_2)-$ moieties is optionally substituted by a $C_{1-6}$ alkyl group.

$R_6$ and $R_{6a}$, which may be the same or different, are each hydrogen, $C_{1-6}$ alkyl, $-CH_2OR_{6b}$, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, thiol, $C_{1-6}$ alkylthio, $-O-\overset{O}{\overset{\|}{C}}-R_{6c}$, $-NHCOR_{6d}$, $-NHSO_2R_{6e}$, $-CH_2SO_2NR_{6f}R_{6g}$, in which each of $R_{6b}$ to $R_{6g}$ is independently hydrogen, $C_{1-6}$ alkyl, aryl or aralkyl;

with the proviso that $R_4$, $R_5$, $R_6$ and $R_{6a}$ are not simultaneously hydrogen;



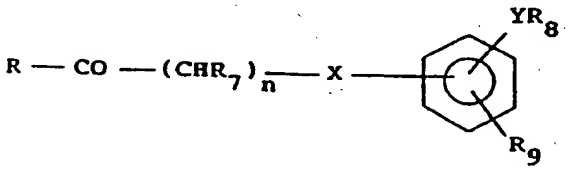
(X)

in which R is as defined in formula (I);

$R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups, or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a hetero-atom;

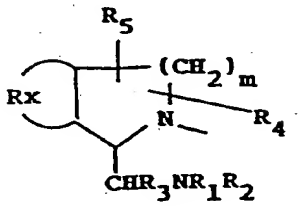
$R_3$ is hydrogen, $C_{1-6}$ alkyl or phenyl, or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

$R_4$ and $R_5$ are independently hydrogen, hydroxyl, halogen, $C_{1-6}$ alkyl or aryl, provided both $R_4$ and $R_5$ are not simultaneously hydrogen: and p is an integer from 1 to 4;



(XI)

in which R represents a group of formula




in which $R_x$ is the remainder of a heterocyclic group, or an optionally substituted phenyl group;

$R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups, or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a hetero-atom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl, or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

$R_4$ and $R_5$, which may be located on the same or different carbon atoms, are independently hydrogen, $C_{1-6}$ alkyl, or phenyl;

m is 1, 2 or 3;

$R_7$ is hydrogen or $C_{1-6}$ alkyl;

n is 0, 1 and 2;

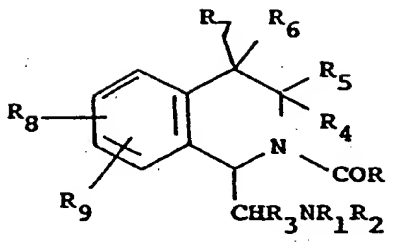
X is direct bond, or O, S or $NR_6$ is hydrogen or $C_{1-6}$ alkyl;

Y is >C=O, >CHOH, >S=O or $>SO_2$;

each of $R_8$ and $R_9$ is $C_{1-6}$ alkyl, or

$R_8$ and $R_9$ are linked together and $R_8$ represents $-(Z)_p-$ where p is 0 or 1 and Z is O, S or $NR_z$ where $R_z$ is hydrogen or $C_{1-6}$ alkyl;

and $R_9$ represents $-(CH_2)_q-$ where q is an integer of from 1 to 4;

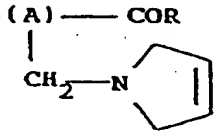


(XII)

in which R is as defined in formula (I) and $R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group optionally substituted with a hetero-atom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl, or $R_3$ together with $R_1$ forms a $-(CH_2)_3-$ or $-(CH_2)_4$, group;
$R_4$ and $R_5$ are identical and are hydrogen or $C_{1-6}$ alkyl, or together form a $C_{2-5}$ linear polymethylene group;
$R_6$ and $R_7$ are indentical and are hydrogen or $C_{1-6}$ alkyl, or together form a $C_{2-5}$ linear polymethylene group;
or $R_5$ and $R_6$ are together $-CH_2-$ when each of $R_4$ and $R_7$ is hydrogen or $C_{1-6}$ alkyl;
with the proviso that $R_4$, $R_5$, $R_6$ and $R_7$ are not simultaneously hydrogen;

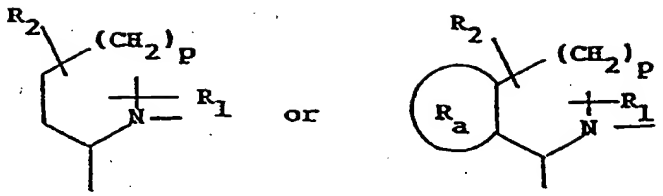
$R_8$ and $R_9$, which may be the same or different, are each hydrogen, $C_{1-6}$ alkyl, $-CH_2OR_{10}$, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, thiol, $C_{1-6}$ alkylthio, $-O\overset{O}{\overset{\|}{C}}R_{11}$, $-NHCOR_{12}$, $-NHSO_2R_{13}$, $-CH_2SO_2NR_{14}R_{15}$, in which each of $R_{10}$ to $R_{15}$ is independently hydrogen, $C_{1-6}$ alkyl, aryl or aralkyl;



(XIII)

in which:

(A) is

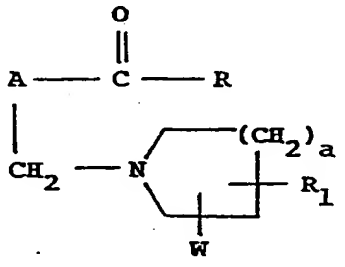


p is 1, 2 or 3;

ROC- is an acyl group linked to the nitrogen atom of group (A) in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

$R_1$ and $R_2$ are substituents on the same or different carbon atoms and are independently hydrogen or $C_{1-6}$ alkyl;

$R_a$ is a fused substituted or unsubstituted heterocyclic or carbocyclic aromatic ring;



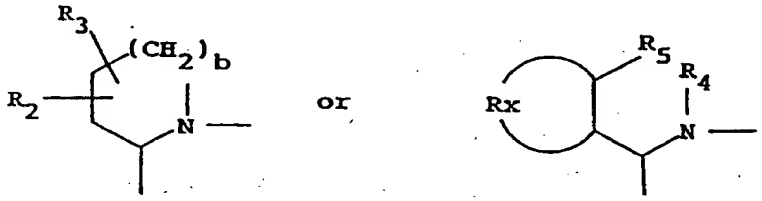
(XIV)

in which W, which may be attached to the same or different carbon atom as $R_1$, is hydroxy, $C_{1-6}$ alkoxy (preferably methoxy), halogen (preferably fluorine), thiol, $C_{1-6}$

alkylthio, hydroxy $C_{1-6}$ alkyl, methylidene, hydroxycarbonyl, aminocarbonyl, $C_{1-3}$ alkoxycarbonyl, $NHR_{1a}$ or $NHCOR_{1a}$ where $R_{1a}$ is H or $C_{1-6}$ alkyl;

$R_1$ is hydrogen, halogen (preferably fluorine), $C_{1-6}$ alkyl (preferably methyl) or together with W forms a keto-group or a cyclic ether or thioether containing from 1 to 4 carbon atoms;

A represents



in which each of $R_2$ and $R_3$, which may be attached to the same or different carbon atom, is hydrogen, $C_{1-6}$ alkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio or halogen (preferably fluorine);

$R_4$ is $C_{1-6}$ alkyl;

$R_5$ is hydrogen or together with $R_4$ forms a $-(CH_2)_c-$ group optionally substituted by one or two $C_{1-6}$ alkyl groups and attached to the same or different carbon atom;

$R_x$ is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;

or $R_x$ is the remainder of an optionally substituted phenyl group;

a is 1 or 2, b is 1, 2 or 3; c is 1, 2 or 3;

and RCO, which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring,

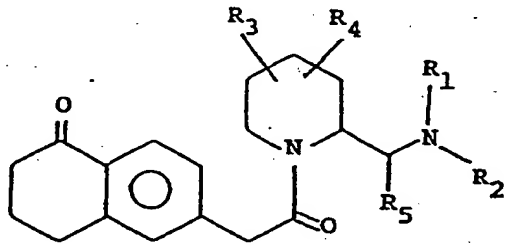
with the provisos that:

i) When A represents,  , R represents a tetralone moiety, or W is halogen or $C_{1-6}$ alkoxy, or $R_1$ is other than hydrogen or a keto group with W;

ii) When $R_2$ is $C_{1-6}$ alkyl, $R_3$ is other than hydrogen;

iii) When $R_x$, $R_4$ and $R_5$ together form an unsubstituted tetrahydroisoquinoline group, R represents a tetralone moiety or $R_1$ is other than hydrogen or a keto group with W, or W is halogen or $C_{1-6}$ alkoxy;

iv) When $R_x$, $R_4$ and $R_5$ together form a substituted tetrahydroisoquinoline group, substitution only occurs in the $-(CH_2)_c-$ group formed by $R_4$ and $R_5$;



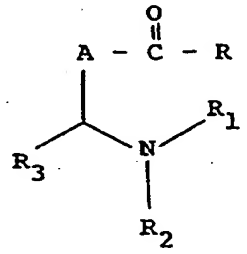
(XV)

in which:

$R_1$ and $R_2$ are each linear or branched $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-4}$ alkenyl, $C_{3-6}$ cycloalkenyl or $C_{3-4}$ alkynyl,

$R_3$ and $R_4$ are identical, and each is hydrogen or $C_{1-4}$ alkyl; and

$R_5$ is hydrogen or $C_{1-3}$ alkyl;



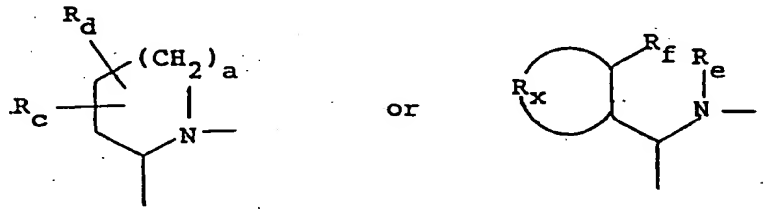
(XVI)

in which:

each of $R_1$ and $R_2$, which may be the same or different, is $C_{1-6}$ alkyl with at least one of them being substituted by at least one of halogen, (preferably fluorine or chlorine), hydroxy, $C_{1-6}$ alkoxy (preferably methoxy), acyloxy (preferably acetoxy), thiol, $C_{1-6}$ alkylthio (preferably methylthio), acylthio (preferably acetylthio) halo-$C_{1-6}$ alkoxy (preferably fluoro-alkoxy), $COR_h$, $COOR_h$, $CONHR_h$ or $NCHOR_h$ where $R_h$ is hydrogen or $C_{1-6}$ alkyl, preferably methyl or ethyl;

$R_3$ is hydrogen or $C_{1-3}$ alkyl, preferably methyl;

A represents



in which each of $R_c$ and $R_d$, which may be attached to the same or different carbon atom, is hydrogen, $C_{1-6}$ alkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio or halogen (preferably fluorine);

$R_e$ is $C_{1-6}$ alkyl;

$R_f$ is hydrogen or together with $R_e$ forms a $-(CH_2)_b-$ group optionally substituted by one or two $C_{1-6}$ alkyl groups and attached to the same or different carbon atom;

$R_x$ is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur; or $R_x$ is the remainder of an optionally substituted or unsubstituted phenyl group;

a is 1, 2 or 3; b is 1, 2 or 3;

and RCO, which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring.

In a further aspect of the invention there is provided a pharmaceutical composition for use in the treatment of inflammation pain in mammals which comprises a compound of formulae (I) to (XVI) (as hereinbefore defined) or a pharmaceutically acceptable salt or solvate thereof, (hereinafter referred to as the Compound) and a pharmaceutically acceptable carrier.

The invention further provides a method for the treatment and/or prophylaxis of inflammation pain in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of the Compound.

The Compounds may be prepared as described in the aforementioned documents, EP-A-228246, 232612, 232989, 260041, 261842, 275696, 330360, 333315, 333427, 361791, 370732, 409489, WO 91/08205, WO 91/08206, WO 91/17116 and WO 91/17981 (the subject matter of which is incorporated herein by reference) or by analogous methods thereto.

Medicaments and compositions containing the Compounds may be prepared by admixture of a Compound with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for the treatment of inflammation pain.

Preferably, a medicament or pharmaceutical composition of

The Compound is in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the Compound.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of the Compound in the form of a pharmaceutically acceptable salt include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

An example of the Compound in the form of a pharmaceutically acceptable solvate includes a hydrate.

The Compounds have at least one asymmetric centre and therefore exist in more than one stereoisomeric form. The invention extends to the use of all such forms and to mixtures thereof, including racemates.

dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if

desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The Compounds may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example, for rectal administration as a suppository or for topical administration as a cream or lotion. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle

from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The effective dose of Compound depends on the particular Compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

Within the above indicated dosage range, no adverse toxicological effect are observed with the Compounds in tests which are indicative of compounds of potential use in treating inflammation pain.

The effects of the Compounds in protecting against inflammation pain may be demonstrated using the paw pressure test in the monoarthritic rat as described in Eur. J. Pharm. 155, 255-264, 1988.

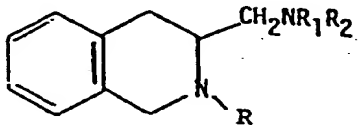
Following subcutaneous administration, the Compounds produce an enhanced analgesic effect in the inflamed paw compared to the non-inflamed paw. The analgesic effect in the inflamed paw is completely reversed by a low intraplantar dose of the opioid antagonist, naloxone, but not by a similar dose of naloxone administered subcutaneously.

Examples of preferred Compounds are:
4-(pyrrolidin-1-yl)methyl-5-(3,4-dichlorophenyl) acetyl-4,5,6,7-tetrahydroimidazo [4,5-c] pyridine (Example 23 of EP-A-333427);
(2)-1-(4-trifluoromethyl phenylacetyl)-2-(1-pyrrolidinyl methyl) piperidine (Example 3 of EP-A-260 041);
and
(2S)-1-[1-oxo-3,4,-dihydro-(2H)-naphth-6-yl]acetyl-2-dimethylaminomethyl piperidine hydrochloride (Example No. 1 of WO 91/17116).

Example 23 of EP-A-333427 shows no evidence of brain penetration by comparing cerebral and plasma levels after subcutaneous administration (1 mg/Kg) of the testing drug. This property, which is in agreement with the very low lipophilicity of the compound [assessed by measuring the $\Delta$logP=logP(n-octanol/acq. buffer) - logP (cyclohexane/acq. buffer) = 4.12 at pH=12, 25°C], renders the compound particularly suitable for obtaining a peripherally selective antinociceptive action.

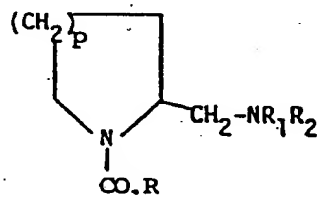
**Claims**

1. Use of a compound, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of inflammation pain, wherein the compound is selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV) or (XVI):



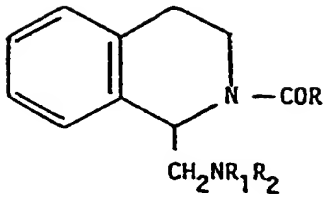
(I)

in which R is an acyl group containing a substituted or unsubstituted carbocyclic or heterocyclic aromatic ring and $R_1$ and $R_2$ are independently $C_{1-6}$ alkyl groups or together form a $C_{3-6}$ polymethylene or alkenylene group;



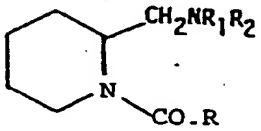
(II)

in which R, $R_1$ and $R_2$ are as defined for formula (I), and p is 1, 2, 3 or 4;



(III)

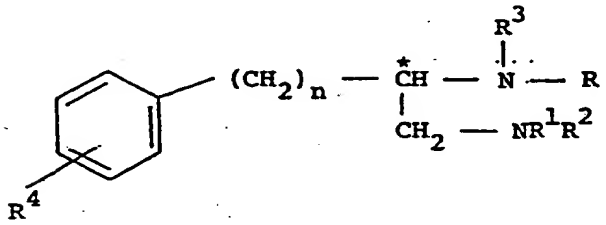
in which R, $R_1$ and $R_2$ and as defined for formula (I);



(IV)

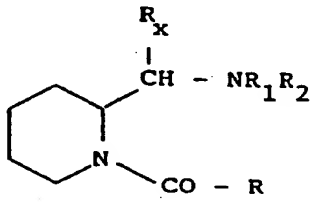
in which R is a group:

in which $R_3$ is Br, $NO_2$ or $CF_3$; and $R_1$ and $R_2$ are as defined in formula (I);



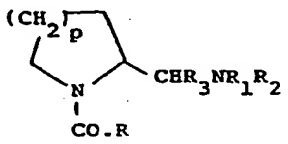
(V)

in which R is as defined in formula (I);
$R^1$ and $R^2$ each independently represents an alkyl, alkenyl or alkynyl group or $R^1$ together with $R^2$ represents a $C_{3-6}$ polymethylene or alkenylene group;
$R^3$ represents hydrogen or alkyl;
$R^4$ represents hydrogen, halogen, alkyl, hydroxy, alkoxy, nitrile, nitro, amino or mono or disubstituted amino;
and
n represents 0 or 1;




(VI)

in which R is as defined in formula (I);
$R_1$ and $R_2$ are independenlty hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{4-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl or together form a $C_{2-6}$ polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a hetero-atom, provided that $R_1$ and $R_2$ are not simultaneously hydrogen;
Rx is $C_{1-6}$ alkyl or phenyl, or Rx together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;



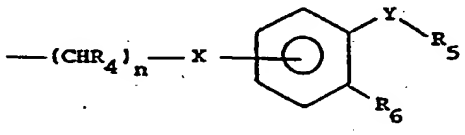

(VII)

in which $R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups, or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group optionally substituted with a hetero-atom, provided that $R_1$ and $R_2$ are not simultaneously hydrogen;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl, or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

p is 1, 2, 3 or 4, and

R is a group of formula



in which the group $-(CH_4)_n-X-$ is in the meta- or para-position with respect to $YR_5$ or $R_6$, $R_4$ is hydrogen or $C_{1-6}$ alkyl;

n is 0, 1 or 2;

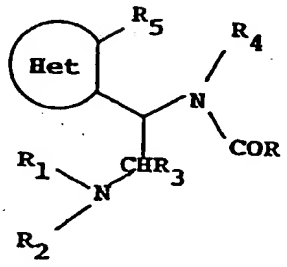
X is a direct bond, or O, S or $NR_a$ in which $R_a$ is hydrogen or $C_{1-6}$ alkyl;

Y is >C=O, >CHOH.>S=O or $>SO_2$;

each of $R_5$ and $R_6$ is $C_{1-6}$ alkyl, or

$R_5$ and $R_6$ are linked together and $R_5$ represents $-(Z)_m-$ where m is 0 or 1 and Z is O, S or $NR_7$ where $R_7$ is hydrogen or $C_{1-6}$ alkyl;

and $R_6$ represents $-(CH_2)_q-$ where q is an integer of from 1 to 4, and in which one or more of the $-(CH_2)-$ groups is optionally substituted by a $C_{1-6}$ alkyl group;




(VIII)

in which R is as defined in formula (I)

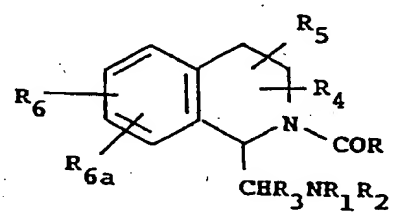
$R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a heteroatom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

$R_4$ is $C_{1-6}$ alkyl, or phenyl;

$R_5$ is hydrogen or together with $R_4$ forms a $-(CH_2)_n-$ group in which n = 1, 2 or 3; and

'Het' is an optionally substituted single or fused ring heterocyclic group, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;




(IX)

in which R is as defined in formula (I) and $R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group optionally substituted with a hetero-atom;

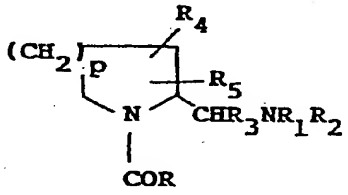
$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl or $R_3$ together with $R_1$ forms a $-(CH_2)_3-$ or $-(CH_2)_4-$, group;

$R_4$ and $R_5$, which may be the same or different and may be attached to the same or different carbon atoms of the isoquinoline nucleus, are each hydrogen, halogen, hydroxy, $C_{1-6}$ alkyl, aryl, or $R_4$ together with $R_5$ form a $-(CH_2)_p$ group, where p is an integer of from 1 to 5 and one or more of the $-(CH_2)-$ moieties is optionally substituted by a $C_{1-6}$ alkyl group.

$R_6$ and $R_{6a}$, which may be the same or different, are each hydrogen, $C_{1-6}$ alkyl, $-CH_2OR_{6b}$, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, thiol, $C_{1-6}$ alkylthio,

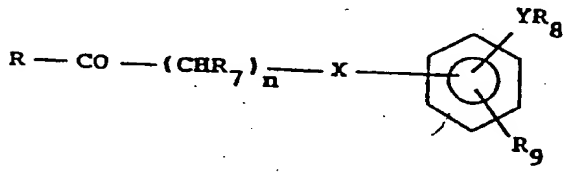
$-O-\overset{O}{\overset{\|}{C}}-R_{6c}$, $-NHCOR_{6d}$, $-NHSO_2R_{6e}$, $-CH_2SO_2NR_{6f}R_{6g}$, in which each of $R_{6b}$ to $R_{6g}$ is independently hydrogen, $C_{1-6}$ alkyl, aryl or aralkyl;

with the proviso that $R_4$, $R_5$, $R_6$ and $R_{6a}$ are not simultaneously hydrogen;



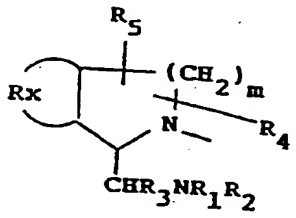

(X)

in which R is as defined in formula (I);
$R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups, or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a hetero-atom;
$R_3$ is hydrogen, $C_{1-6}$ alkyl or phenyl, or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;
$R_4$ and $R_5$ are independently hydrogen, hydroxyl, halogen, $C_{1-6}$ alkyl or aryl, provided both $R_4$ and $R_5$ are not simultaneously hydrogen: and p is an integer from 1 to 4;



(XI)

in which R represents a group of formula



in which $R_x$ is the remainder of a heterocyclic group, or an optionally substituted phenyl group;

$R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups, or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group, optionally substituted with a hetero-atom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl, or $R_3$ together with $R_1$ form a $-(CH_2)_3-$ or $-(CH_2)_4-$ group;

$R_4$ and $R_5$, which may be located on the same or different carbon atoms, are independently hydrogen, $C_{1-6}$ alkyl, or phenyl;

m is 1, 2 or 3;

$R_7$ is hydrogen or $C_{1-6}$ alkyl;

n is 0, 1 and 2;

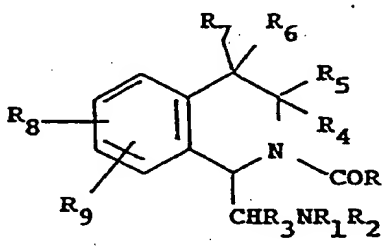
X is direct bond, or O, S or $NR_6$ is hydrogen or $C_{1-6}$ alkyl;

Y is >C=O, >CHOH, >S=O or $>SO_2$;

each of $R_8$ and $R_9$ is $C_{1-6}$ alkyl, or

$R_8$ and $R_9$ are linked together and $R_8$ represents $-(Z)_p-$ where p is 0 or 1 and Z is O, S or $NR_z$ where $R_z$ is hydrogen or $C_{1-6}$ alkyl;

and $R_9$ represents $-(CH_2)_q-$ where q is an integer of from 1 to 4;



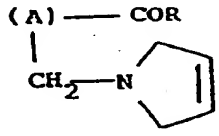

(XII)

in which R is as defined in formula (I) and $R_1$ and $R_2$ are independently hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{4-12}$ cycloalkylalkyl groups or together form a $C_{2-8}$ branched or linear polymethylene or $C_{2-6}$ alkenylene group optionally substituted with a hetero-atom;

$R_3$ is hydrogen, $C_{1-6}$ alkyl, or phenyl, or $R_3$ together with $R_1$ forms a $-(CH_2)_3-$ or $-(CH_2)_4$, group;
$R_4$ and $R_5$ are identical and are hydrogen or $C_{1-6}$ alkyl, or together form a $C_{2-5}$ linear polymethylene group;
$R_6$ and $R_7$ are indentical and are hydrogen or $C_{1-6}$ alkyl, or together form a $C_{2-5}$ linear polymethylene group;
or $R_5$ and $R_6$ are together $-CH_2-$ when each of $R_4$ and $R_7$ is hydrogen or $C_{1-6}$ alkyl;
with the proviso that $R_4$, $R_5$, $R_6$ and $R_7$ are not simultaneously hydrogen;

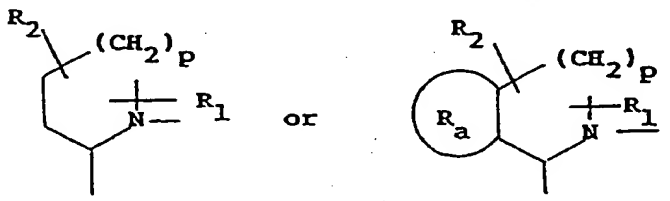
$R_8$ and $R_9$, which may be the same or different, are each hydrogen, $C_{1-6}$ alkyl, $-CH_2OR_{10}$, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ alkoxycarbonyl, thiol, $C_{1-6}$ alkylthio,

$-O\overset{O}{\overset{\|}{C}}R_{11}$, $-NHCOR_{12}$, $-NHSO_2R_{13}$, $-CH_2SO_2NR_{14}R_{15}$, in which each of $R_{10}$ to $R_{15}$ is independently hydrogen, $C_{1-6}$ alkyl, aryl or aralkyl;



(XIII)

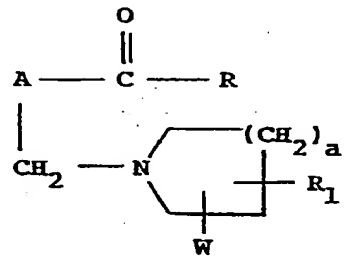
in which:
(A) is



p is 1, 2 or 3;
ROC- is an acyl group linked to the nitrogen atom of group (A) in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring;

$R_1$ and $R_2$ are substituents on the same or different carbon atoms and are independently hydrogen or $C_{1-6}$ alkyl;

$R_a$ is a fused substituted or unsubstituted heterocyclic or carbocyclic aromatic ring;

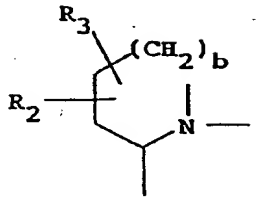


(XIV)

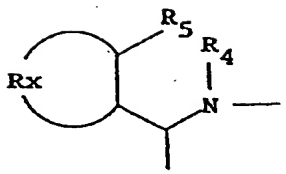
in which W, which may be attached to the same or different carbon atom as $R_1$, is hydroxy, $C_{1-6}$ alkoxy (preferably methoxy), halogen (preferably fluorine), thiol, $C_{1-6}$ alkylthio, hydroxy $C_{1-6}$ alkyl, methylidene, hydroxycarbonyl, aminocarbonyl, $C_{1-3}$ alkoxycarbonyl, $NHR_{1a}$ or $NHCOR_{1a}$ where $R_{1a}$ is H or $C_{1-6}$ alkyl;

$R_1$ is hydrogen, halogen (preferably fluorine), $C_{1-6}$ alkyl (preferably methyl) or together with W forms a keto-group or a cyclic ether or thioether containing from 1 to 4 carbon atoms;

A represents




or




in which each of $R_2$ and $R_3$, which may be attached to the same or different carbon atom, is hydrogen, $C_{1-6}$ alkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio or halogen (preferably fluorine);

$R_4$ is $C_{1-6}$ alkyl;

$R_5$ is hydrogen or together with $R_4$ forms a $-(CH_2)_c-$ group optionally substituted by one or two $C_{1-6}$ alkyl groups and attached to the same or different carbon atom;

$R_x$ is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur;

or $R_x$ is the remainder of an optionally substituted phenyl group;

a is 1 or 2, b is 1, 2 or 3; c is 1, 2 or 3;

and RCO, which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring,

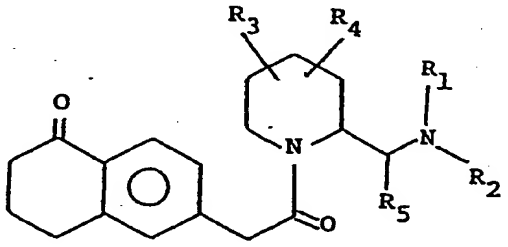
with the provisos that:

i) When A represents, N-, R represents a tetralone moiety, or W is halogen or $C_{1-6}$ alkoxy, or $R_1$ is other than hydrogen or a keto group with W;

ii) When $R_2$ is $C_{1-6}$ alkyl, $R_3$ is other than hydrogen;

iii) When $R_x$, $R_4$ and $R_5$ together form an unsubstituted tetrahydroisoquinoline group, R represents a tetralone moiety or $R_1$ is other than hydrogen or a keto group with W, or W is halogen or $C_{1-6}$ alkoxy;

iv) When $R_x$, $R_4$ and $R_5$ together form a substituted tetrahydroisoquinoline group, substitution only occurs in the $-(CH_2)_c-$ group formed by $R_4$ and $R_5$;

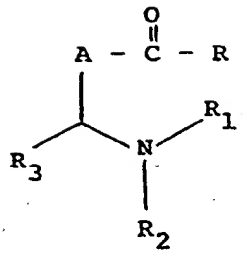



(XV)

in which:

$R_1$ and $R_2$ are each linear or branched $C_{1-4}$ alkyl, $C_{3-6}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-4}$ alkenyl, $C_{3-6}$ cycloalkenyl or $C_{3-4}$ alkynyl,
$R_3$ and $R_4$ are identical, and each is hydrogen or $C_{1-4}$ alkyl; and

$R_5$ is hydrogen or $C_{1-3}$ alkyl;



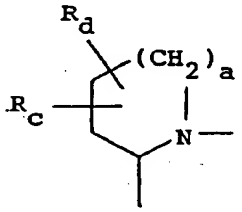
(XVI)

in which:

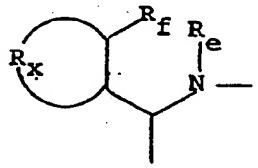
each of $R_1$ and $R_2$, which may be the same or different, is $C_{1-6}$ alkyl with at least one of them being substituted by at least one of halogen, (preferably fluorine or chlorine), hydroxy, $C_{1-6}$ alkoxy (preferably methoxy), acyloxy (preferably acetoxy), thiol, $C_{1-6}$ alkylthio (preferably methylthio), acylthio (preferably acetylthio) halo-$C_{1-6}$ alkoxy (preferably fluoro-alkoxy), $COR_h$, $COOR_h$, $CONHR_h$ or $NCHOR_h$ where $R_h$ is hydrogen or $C_{1-6}$ alkyl, preferably methyl or ethyl;

$R_3$ is hydrogen or $C_{1-3}$ alkyl, preferably methyl;

A represents



or



in which each of $R_c$ and $R_d$, which may be attached to the same or different carbon atom, is hydrogen, $C_{1-6}$ alkyl, hydroxy, thiol, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio or halogen (preferably fluorine);

$R_e$ is $C_{1-6}$ alkyl;
$R_f$ is hydrogen or together with $R_e$ forms a $-(CH_2)_b-$ group optionally substituted by one or two $C_{1-6}$ alkyl groups and attached to the same or different carbon atom;
$R_x$ is the remainder of an optionally substituted single or fused ring heterocyclic group, preferably having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from oxygen, nitrogen and sulphur; or $R_x$ is the remainder of an optionally substituted or unsubstituted phenyl group;

a is 1, 2 or 3; b is 1, 2 or 3;

and RCO, which is linked to the nitrogen atom of the group A, is an acyl group in which the group R contains a substituted or unsubstituted carbocyclic aromatic or heterocyclic aromatic ring.

2. A use according to claim 1 in which the compound is selected from:

4-(pyrrolidin-1-yl)methyl-5-(3,4-dichlorophenyl) acetyl-4,5,6,7-tetrahydroimidazo [4,5-c] pyridine;
(2)-1-(4-trifluoromethyl phenylacetyl)-2-(1-pyrrolidinyl methyl)piperidine;
and
(2S)-1-[1-oxo-3,4,-dihydro-(2H)-naphth-6-yl]acetyl-2-dimethylaminomethyl piperidine hydrochloride.

3. A pharmaceutical composition for use in the treatment of inflammation pain in mammals, which comprises a

compound of formulae (I) to (XVI) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

4. A method for the treatment and/or prophylaxis of inflammation pain in mammals, which comprises administering to a mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formulae (I) to (XVI) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/00838

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/165 A 61 K 31/38 A 61 K 31/40
A 61 K 31/44 A 61 K 31/55 A 61 K 31/34 A 61 K 31/35 A 61 K 31/445
A 61 K 31/47 A 61 K 31/54

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0333427 (ZAMBELETTI S.p.A.) 20 September 1989, see abstract, pages 1-2; page 3, lines 1-16; page 24, example 23 --- | 1-4 |
| X | EP,A,0260041 (ZAMBELETTI S.p.A.) 16 March 1988, see abstract, pages 1-2; page 3, lines 1-11; pages 8-9, lines 43-15, example 3 --- | 1-4 |
| P,X | WO,A,9117116 (ZAMBELETTI S.p.A.) 14 November 1991, see abstract; page 1, lines 1-12; example 1, page 13 --- | 1-4 |
| X | EP,A,0330461 (GLAXO GROUP LTD) 30 August 1989, see page 2, lines 1-47 --- | 1-4 |
| X | EP,A,0330467 (GLAXO GROUP LTD) 30 August 1989, see page 2, lines 1-46 --- -/- | 1-4 |

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 26-06-1992 | 21. 09. 92 |
| International Searching Authority: EUROPEAN PATENT OFFICE | Signature of Authorized Officer: Jacques Traas |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS C NSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | EP,A,0380063 (WARNER-LAMBERT) 1 August 1990, see abstract; page 6, lines 50-58 | 1-4 |
| X | Journal of Medicinal Chemistry, vol. 34, no. 1, January 1991, American Chemical Society, V. VECCHIETTI et al.: "(2S)-1-(arylacetyl)-2-(aminomethyl)piperidine derivatives: novel, highly selective kappa opioid analgesics", pages 397-403, see abstract | 1-4 |
| X | EP,A,0374756 (MERCK) 27 June 1990, see page 3, lines 6-18; claims | 1,3,4 |
| A | European Journal of Pharmacology, vol. 190, no. 3, 13 November 1990, Elsevier Science Publishers B.V. (Biomedical Division), T. PELISSIER et al.: "Analgesia produced by intrathecal administration of the kappa opioid agonist, U-50,488H, on formalin-evoked cutaneous pain in the rat", pages 287-293, see abstract; discussion | 1-4 |
| A | The Journal of Pharmacology and Experimental Therapeutics, vol. 236, no. 1, January 1986, The American Society for Pharmacology and Experimental Therapeutics, (US), G.F. STEINFELS et al.: "Antinociceptive profiles of mu and kappa opioid agonists in a rat tooth pulp stimulation procedure", pages 111-117, see abstract; page 112, column 2, paragraph 2; page 114, figure 4; page 115, column 2, paragraph 2 | 1-4 |
| A | European Journal of Pharmacology, vol. 151, no. 3, 1988, Elsevier Science Publishers B.V. (Biomedical Division), G.F. COSTELLO et al.: "A novel series of potent and selective agonists at the opioid kappa-receptor", pages 475-478, see the whole document, especially figure 1; pages 477-478: "Discussion" | 1-4 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/00838

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIM 4 IS DIRECTED TOWARDS A METHOD OF TREATMENT OF THE HUMAN/ANI MAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUNDS.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200838 SA 58919

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/09/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP-A- 0333427 | 20-09-89 | AU-A- 3131589 | 21-09-89 |
| | | JP-A- 2101062 | 12-04-90 |
| | | US-A- 4999359 | 12-03-91 |
| EP-A- 0260041 | 16-03-88 | AU-B- 601763 | 20-09-90 |
| | | AU-A- 7771187 | 10-03-88 |
| | | JP-A- 63146860 | 18-06-88 |
| | | US-A- 4826819 | 02-05-89 |
| WO-A- 9117116 | 14-11-91 | AU-A- 7681491 | 27-11-91 |
| EP-A- 0330461 | 30-08-89 | AU-A- 3029589 | 24-08-89 |
| | | JP-A- 1308250 | 12-12-89 |
| EP-A- 0330467 | 30-08-89 | JP-A- 2138254 | 28-05-90 |
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| | | CA-A- 2008391 | 24-07-90 |
| | | JP-A- 2233669 | 17-09-90 |
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| EP-A- 0374756 | 27-06-90 | DE-A- 3935371 | 05-07-90 |
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| | | CA-A- 2006413 | 23-06-90 |
| | | JP-A- 2215769 | 28-08-90 |

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82